LIST OF CEHS STANDARD PILOT PROJECTS AWARDS 2014-2015
(Each award is for $25,000)

PPP AWARD 2014-01

Project Title: A Novel Role for UV-generated sedDNAs in Inflammation and Autoimmunity.
P.I.: Michael Kemp, Ph.D., Research Assistant Professor; Biochemistry and Biophysics, SoM.

Abstract

The mechanism by which ultraviolet (UV) light aggravates the symptoms of the autoimmune disorder lupus erythematous (LE) is not clear. This is a problem because it signifies a lack of understanding of LE photosensitivity and represents a barrier to predicting patient disease outcomes. The *objective* of this interdisciplinary, collaborative pilot project is to examine how the small, excised, damage-containing DNA oligonucleotide (sedDNA) products of UV photoproduct repair impact the aberrant inflammatory and immune response pathways that define LE and to determine whether cutaneous LE patients develop autoantibodies against the proteins and sedDNAs that are involved in these signaling processes. The *central hypothesis* is that the association of sedDNAs with specific pattern recognition receptor proteins (PRRs) leads to the overstimulation or amplification of the autoimmune response in the skin of LE patients. Ultimately, this research has the potential to improve our understanding of LE patient photosensitivity and lead to the development of new tools for diagnosing, classifying, and treating LE patient subtypes. The preliminary data generated here will be used by Dr. Kemp to apply for R01-level funding.

PPP AWARD 2014-02

Project Title: Effect of gene-nutrient interaction on the variation in serum uric acid levels
P.I.: V. Saroja Voruganti, Assistant Professor of Nutrition

Abstract

Uric acid is the end product of purine metabolism in humans. Elevated serum uric acid (SUA) or hyperuricemia increases the risk for diseases such as gout, hypertension, chronic kidney disease and cardiovascular disease. Hyperuricemia in children is an indicator of adult onset hypertension and cardiovascular risk. Several studies have been conducted to identify genetic loci that may affect SUA. However, none of these studies have been conducted in children or investigated the effects of gene by environment interaction on SUA. Given the important role of nutrients in SUA regulation, we propose to identify and characterize putative functional variants that interact with nutrients to influence SUA levels in children. To achieve this goal we have the following specific aims: i) Identify variation in transcribed regions of genes that are associated with SUA levels; and 2) Determine the effect of interaction of the functional variants with nutrients on SUA levels. This study will reveal functional variants that interact with nutrients to influence serum uric acid in children and provide novel targets for treating these painful diseases by dietary interventions early in life.

PPP AWARD 2014-03

Project Title: Molecular Tags for high sensitivity quantification of mutations in amplicon and DNA capture protocols.
P.I.: Piotr Mieczkowski, PhD, Research Assistant Professor, Genetics

Abstract

Targeted sequencing gives the promise of sensitive and quantative measurement and monitoring of mutations in several assays including the free circulation DNA (fc DNA) in peripheral blood. From a diagnostic perspective, the fc DNA can carry information about tumor burden[12-17], virus load (EBV[19-27] and HPV[28-33]) as well as mutation loads in cells which underwent apoptosis, necrosis, or were eliminated by the Immune system. To acquire all this information from the fc DNA sequencing data, we need to improve our strategy for Next Generation Sequencing assays to increase the sensitivity of variant detection. Currently, a PCR artifacts and an error rate produced from the DNA sequencing technology (10^3) affects the sensitivity of Amplicon Sequencing assays. Additionally, the Whole Genome Sequencing or the DNA capture technology requires a high coverage for variant discovery to reduce false discovery rate sbased on sequencing data. Both of these applications are unable to confidently call variants lower than those of a frequency level of 0.1%. Introducing the Molecular Tags (Duplex tags), used for low DNA input samples like the fc DNA, finally allow for high sensitivity variant detection for both Amplicon and DNA capture assays.

PPP AWARD 2014-04

Project Title: Discovery of New Detoxification Pathways Using System Biology of Liver Cultures
P.I.: Jeffrey M. Macdonald, PhD, Associate Professor of Biomedical Engineering, SoM

Abstract

A novel system biology approach combining fluxomics with targeted kinomics will be applied to test the hypothesis that substrate cycles, aka futile cycles, are detoxification mechanisms designed to protect the cell from excess redox energy and subsequent generation of reactive oxygen species. Substrate cycling can dissipate an overloaded mitochondrial proton motive force generated by the electron transport chain by consuming NADH or shuttling it to the cytosol. This action regulates redox balance and maintains constant energy flow, similar to how a linear regulator maintains constant voltage in an electrical circuit. A unique ^{13}C-labeling strategy encodes metabolic memory in specific ^{13}C-metabolites enabling quantification of substrate cycles. The response of 2D and 3D cultures of hepatocytes to two toxicants, ethanol, and acetaldehyde, will test the hypothesis. A multidisciplinary team consisting of Directors from four CEHS Cores of Drs. Macdonald (Systems Biology; Metabolomics), Graves (Proteomics), and Bodnar (Biomarkers), will supervise the acquisition of fluxomics/metabolomics, targeted kinomics and targeted metabolite data, respectively, from 2D and 3D hepatocytes cultures (Dr. LeCluyse, Hamner Institute). Dr. Gomez (UNC, SOM), will develop a mechanistic metabolic flux analysis (MFA) model to interpret the dataset.